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| 10/801,517 | 03/16/2004 | Xiaoyang Qi | 0010872.0556916 | 4062 |

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| EXAMINER | |
|---|---|
| SANG, HONG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 07/10/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@fbtlaw.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/801,517 | QI, XIAOYANG | |
| | Examiner | Art Unit | |
| | HONG SANG | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *9-49 and 58-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

**RE: Qi**

1. Applicant's response filed on 4/29/2009 is acknowledged. Claims 1-65 are pending. Claims 9-49 and 58-65 have been withdrawn from consideration as being drawn to non-elected inventions. Claims 1 and 50 have been amended.

2. Claims 1-8, and 50-57 are under examination. Due to restriction and species election, claims are examined to the extent that the structure analog of phosphatidylserine is dioleoylphosphatidylserine (DOPS).

***Objections Withdrawn***

3. The objection to claims 1-8 for reciting "wherein the phospholipid forms a nanovesicle having the polypeptide embedded within its polypeptide embedded nanovesicle" is withdrawn in view of applicant's amendment to the claims.

***Rejections Withdrawn***

4. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph because the phrases "wherein the polypeptide comprises H1 through H5 helix regions of saposin C and retains plasma membrane affinity" recited in claim 1, and "wherein the polypeptide includes sequences which form helix regions H1 and H5 of saposin C, which embed within the lipid bilayer of the nanovesicle" recited in claim 50 are new matter is withdrawn in view of applicant's amendment to the claims

***Rejections Maintained***

***Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)***

5. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

The response states that applicants have amended the claims to provide for "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity". The response states that the saposin fold comprises five alpha-helices (H1 through H5), which are responsible for proper orientation within the phospholipid bilayer of the nanovesicles and further comprise the enzyme activation of domain of amino acids 48-62, which span helices H3 and H4.

Applicant's arguments have been carefully considered but are not persuasive. Qi et al (J. Biol. Chem., 2001, 276 (29):27010-27017, IDS) disclose that the "saposin fold" is a common fold in a single globular structure for all the saposins and saposin like proteins and domains (see page 27010, column 2, paragraph 2). Qi et al disclose that despite the shared saposin-fold structure in solutions, saposin and saposin-like proteins have diverse *in vivo* biological functions (see page 27010, column 2, paragraph 3). Liepinsh et al (Nature Structural Biol., 1997, 4(10): 793-795) disclose several saposin and saposin-like proteins having a common "saposin fold" but different functions (see Figure 1). It is noted that the saposin fold in different proteins has a different amino acid sequence (see Figure 1). Therefore, conservation of a saposin fold is not conservation of an amino acid sequence, or a function. Furthermore, Qi et al (J. Biol. Chem., 1996, 271(12): 6874-6880, submitted by applicants on 10/31/2008) disclose that although

molecular modeling and site-directed mutagenesis localized the activation of properties of saposin C to the regions spanning residue 47-62, secondary structure was need for retention of this property (see abstract). The new limitation "the polypeptide comprises a saposin fold" recited in the claims does not require the claimed polypeptide to have the sequence of the H1-through H5 region of saposin C. The claimed variants include substitution, deletion and addition of amino acids at any residues as long as the saposin fold is conserved, and the substitution is conservative (see claim 1 step (b), or the resulting variants are at least 95% identical of SEQ ID NO:2 (see claim 1, step (a)). However, as discussed above, conservation of a saposin fold is not conservation of anti-tumor activity. The specification does not provide adequate written description regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity. Based on the unpredictability of protein chemistry, and lack of written description, those of ordinary skill in the art would not be able to envision the detailed structures of the encompassed variants, as such one skilled in the art would reasonable conclude that the applicant was not in possession of the broadly claimed variants. For these reasons, the rejection is maintained.

***Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)***

6. The rejection of claims 1-8, and 50-57 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine,

phosphatidylethanolamine and structural analog thereof, and a polypeptide of SEQ ID NO.2, does not reasonably provide enablement for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2, or a polypeptide of SEQ ID NO:2 having one or more conservative substitutions is maintained.

The response states that applicants have amended the claims to provide for "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity". The response states that the saposin fold comprises five alpha-helices (H1 through H5), which are responsible for proper orientation within the phospholipid bilayer of the nanovesicles and further comprise the enzyme activation of domain of amino acids 48-62, which span helices H3 and H4. The response states that it would not require undue experimentation to perform the invention as claimed.

Applicant's arguments have been carefully considered but are not persuasive. As discussed above, conservation of a saposin fold is not conservation of amino acid sequence, or a function. Furthermore, Qi et al (J. Biol. Chem., 1996, 271(12): 6874-6880, submitted by applicants on 10/31/2008) disclose that although molecular modeling and site-directed mutagenesis localized the activation of properties of saposin C to the regions spanning residue 47-62, secondary structure was need for retention of this property (see abstract). The new limitation "the polypeptide comprises a saposin fold" recited in the claims does not require the claimed polypeptides to have the sequence of the H1-through H5 region of saposin C. The claimed variants include

substitution, deletion and addition of amino acids at any residues as long as the saposin fold is conserved, and the substitution is conservative (see claim 1 step (b), or the resulting variants are at least 95% identical of SEQ ID NO:2 (see claim 1, step (a)). However, as discussed above, conservation of a saposin fold is not conservation of an anti-tumor activity. The specification does not provide adequate written description regarding which amino acids and how many of them can be changed in the wild type saposin C such that the resulting variants still have the anti-tumor activity. In view of the unpredictability of protein chemistry, and lack of written description, those of ordinary skill in the art would not be able to envision the detailed structure of the encompassed variants. Therefore, it would require undue experimentation to make the broadly claimed variants having the required anti-tumor activity. For these reasons, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

7. The rejection of claims 1-8 and 50-57 under 35 U.S.C. 103(a) as being unpatentable over O'Brien (US 5,700,909, Date of Patent: 12/23/1997), in view of Liu et al. (WO 98/33482, Pub. date: 8/6/1998), and Habberfield (US 2002/0099001A1, Pub Date: 7/25/2002, earlier effective filing date 2/1/1995) is maintained.

The response states that although O'Brien discloses that the liposome encapsulation technology is well known, it is clear the treatment does not require the liposomes. The response states that the O'Brien patent cited claims for peptides from the first part of the peptide, not the full saposin C or the prosaposin. The response

states that Habberfield and Liu claimed that the encapsulation step is required for the drug delivery by the liposomes containing DOPS, in applicant's application, Saposin C couples with the DOPS liposome by embedding its N- and C-terminal sequences into the lipid bilayer.

Applicant's arguments have been carefully considered but are not persuasive. O'Brien teaches a method of treatment of demyelination disorders in mammal comprising administering to the mammal a pharmaceutically effective amount of saposin C, wherein the saposin C may be advantageously enclosed in a liposome-like (lamellar) structure (see column 4, lines 48-63, and column 9, lines 52-59). O'Brien discloses that the saposin C is the entire protein of saposin C or a peptide comprising amino acids 8-29 of saposin C (see column 4, lines 39-42). As such O'Brien teaches saposin C (entire protein) enclosed in liposome. While O'Brien does not teach that the liposome is made of phosphatidylserine (PS), dioleoylphosphatidylserine (DOPS), or phosphatidylethanolamine (PE), these deficiencies are made up for in the teachings of Liu and Habberfield. Liu et al. teach encapsulation of a drug in liposome vesicle composed of PE and PS. Habberfield teaches liposomes composed of DOPS for drug delivery (see paragraph 0027). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the liposome composed of PS such as DOPS or PE to encapsulate saposin C with the molar ratio taught by Liu for the treatment of demyelination disorders in view of the teachings of Liu and Habberfield. One of ordinary skill in the art would have been motivated to do so because PS such as DOPS and PE were wildly used for making drug delivery

liposomes as shown by the teachings of Liu and Habberfield. Although the cited references do not teach that Saposin C couples with the DOPS liposome by embedding its N- and C-terminal sequences into the lipid bilayer, it is considered as inherent property of Saposin C, as evidence by Qi et al (J. Biol. Chem., 2001, 276 (29):27010-27017, IDS). Qi et al disclose that amphipathic helices at the amino- and carboxyl termini of saposins A and C were shown to insert into the lipid bilayer to about five carbon bond leng6hs (see abstract and Figure 7). Moreover, the Saposin C enclosed in DOPS liposome would have the antitumor activity because it has the required active components i.e. saposin C and DOPS. Because of these reasons, the rejection is deemed proper and is therefore maintained.

***Double Patenting***

8. The rejection of claims 1-3, and 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

The response states a Terminal Disclaimer will be filed if conflicting claims are issued.

Since no Terminal Disclaimer has been filed, the rejection is maintained.

***New Grounds of Rejections***

***Claim Rejections - 35 USC § 112, 1st paragraph***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-8 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

The phrases "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity" recited in claim 1, and "wherein the polypeptide includes sequences which form a saposin fold, which embed within the lipid bilayer of the nanovesicle" recited in claim 50 are considered new matter since the specification, drawings and claims as filed do not provide clear support for such limitations. In the introduction of the background of the invention, the specification discloses that saposins associate with lipid membranes by embedding into the outer leaflets, and the H-1 and H-5 helices are integral to this process, suggesting that proper membrane interaction of saposin C affects its specificity and activity (see the specification, paragraph [0007]). The specification at paragraph [0006] discloses that all saposins and saposin-like proteins and domains contain a "saposin fold" when in solution. The specification at paragraph [0006] further discloses that despite this shared saposin-fold in solution, saposins and saposin-like proteins have diverse in vivo biological functions in the

enhancement of lysosomal SL and GSL degradation by specific hydrolases. The specification does not contemplate making saposin variants by conserving the structure of a saposin fold.

If applicant believes that support for the above-mentioned phrases or terms is present in the specification, claims or drawing as originally filed, applicant must, in responding to this action, point out with particularity, where such support may be found.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Conclusion***

11. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HONG SANG whose telephone number is (571)272-8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Hong Sang/
Examiner, Art Unit 1643

/Christopher H Yaen/
Primary Examiner, Art Unit 1643